Studies on the Relationship between Peptic Ulcer and the Parathyroid

AUTHOR(S):

WATASE, TSUTOMU

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Studies on the Relationship between Peptic Ulcer and the Parathyroid

by

TSUTOMU WATASE

From the 2nd Department of Surgery Kanazawa University, Medical School
(Director: Prof. Dr. ICHIO HONJO)

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I. INTRODUCTION

Ulcus rotundum of the stomach and duodenum was first described by GRAVEILLIER[33] in 1823, and he pointed out the participation of gastric juice, particularly significance of hydrochloric acid, in occurrence of ulceration. However, he could not clarify the reason of localized ulceration, despite gastric juice is in contact with the gastric mucous membrane allover. In this respect, various hypotheses have been insisted since VIRCHOW[70], even though satisfactory knowledge is not acquired yet on this point. Numerous studies have been reported up to present concerning gastric hypersecretion and disposition of the gastric wall in gastroduodenal ulceration, still containing many problems to be solved. In general, it is widely accepted that ulcer of the stomach appears on the basis of disproportionate equilibrium of acidity of gastric juice and resistance of the gastric mucous membrane[7)16)43)54)66)]. Particularly, there are many who seek the cause of gastroduodenal ulceration in autodigestion of the gastric mucous membrane due to elevation of acidity of gastric juice [6)20)62)65)]. However, acidity of gastric juice is not always elevated in all cases of peptic ulcer, revealing hypoacidity in some of those cases, in which the cause of ulceration cannot be explained from the elevation of acidity of gastric juice. Hypoacidity of such cases of peptic ulcer is generally interpreted to be due to secondary decrease in acidity of gastric juice caused by an intensely existing concomitant gastritis[54)]. On the other hand, it is assumed that in some instances gastric mucous membrane can possibly receive relatively strong action of gastric juice owing to decrease in neutralization of the acidity or reduction of protecting effect of the mucous membrane.

It is reported that peptic ulcer is frequently observed in cases of hyperparathyroidism [9)59)], without revealing elevation of acidity in gastric juice in most of these cases[71)72)73)]. In such cases, it is considered that significance of ulceration consists in the reduction of resistance of gastroduodenal mucous membrane against hydrochloric acid.

From the clinical observation on the cases of peptic ulcer that gastric juice of these cases does not always reveal hyperacidity, but some of these reveal normo- or hypoacidity, the present studies were attempted to disclose the participation of the parathyroid in peptic ulcer in the aim of clarifying clinically and experimentally the mechanism of peptic ulcer in cases without hyperacidity of gastric juice. Interesting results were obtained.

II. CLINICAL STUDIES

It is said that peptic ulcer is caused by disproportionate equilibrium of acidity of gastric juice and defence of gastric mucous membrane against the acidity[7)16)43)54)66)], and there can be seen many publications emphasizing hyperacidity of gastric juice as the cause of the ulceration[54)62)65)]. However, it is well admitted by clinicians that gastric juice of ulcerative patients do not always reveal hyperacidity[60)]. This is considered to be due to decrease in acidity of gastric juice caused by atrophic change in the area of hydrochloric

acid secretion in gastric mucous membrane caused by concomitantly existing gastritis[54]. However, it is readily considered that in some cases reduction of resistance of gastric mucous membrane is the essential cause of peptic ulceration not simply by such a secondary decrease in the acidity, even though the gastric juice reveals normo- or rather hypoacidity. The author's interest was directed to parathyroid function in these cases. Concerning an occurrence of peptic ulcer associated with parathyroid function, publications are gradually increasing in recent years since the first report of ROGERS[58]. Concerning the mechanism of ulceration in hyperparathyroidism, OSTROW[55] and REIFENSTEIN[57] have made presumption, since the report of ENGEL[24], that parathyroid hormone has proteolytic action on gastric mucous membrane, reducing defence of the membrane with resulting ulceration. At this point, the author of the present experiment carried out the examinations of parathyroid function in patients with peptic ulcer.

1. Materials and Methods

Following examinations were carried out in 191 cases of gastroduodenal ulcer operated on in our clinic during the period of 5 years from 1959 June to 1964 May, existence of ulcer being ascertained in these cases at operation, 13 cases of gastritis for the control study hospitalized during the same period and 22 cases of other miscellaneous diseases (10 cases of stomach cancer, 7 cases considered to be normal from certain labolatory examinations, 2 cases of BANTI's disease, 1 case of appendicitis, 1 case of cholecystitis and 1 case of pancreatitis), 236 cases in all.

i. Determination of Acidity of Gastric Juice

Gastric juice was collected with the lapse of time following the method of KATSCH and KALK[42] and titration of acidity was carried out with N/10 caustic soda. Data of the acidity was classified into three groups of hyperacidity with the maximum value of more than 40 of free hydrochloric acid or more than 60 of total acidity, normoacidity with the maximum value of 20 to 40 of free hydrochloric acid or 40 to 60 of total acidity and hypoacidity with the maximum value of less than 20 of free hydrochloric acid or less than 40 of total acidity.

ii. Determination of Alkaline Secretion of the Stomach

Alkaline secretion of the stomach is also called nonparietal cell secretion, and this is calculated following GLASS[29] by subtracting the value of acidity of free hydrochloric acid from total acidity, average value of which in each fractional material obtained by Katsch and Kalk's method in individual cases being taken as the data.

iii. Examinations of Parathyroid Function

After the method of SONODA[67], following examinations were carried out. Examinations of parathyroid function were performed in 38 cases of peptic ulcer, which was ascertained by operation, 13 cases of gastritis hospitalized during the same period and 22 cases of other diseases, 73 cases in total. All these cases were selected so that the cases of kidney disease, albuminuria or rachitis might not be included.

a) Serum Calcium Level

Serum calcium was determined in the fasting state following the *glyoxalbis method* of GOLDSTEIN[32], normal level of which was 9.0 to 11.5 mg/dl (4.5 to 5.5 mEq/L)[31][34].

b) Serum Non-Organic Phosphorus Level

Serum non-organic phosphorus was also determined in the fasting state following *aminonaphthol sulfonic acid method*[25], normal level of which being 2.4 to 4.4 mg/dl[31)34)].

c) Urinary Calcium Level

Calcium content in total urine during 24 hours was determined following *glyoxalbis method* of GOLDSTEIN[32)], normal level of which being 16 to 321 mg, 158 mg on an average[31)].

d) Urinary Non-Organic Phosphorus Level

Non-organic phosphorus in total urine during 24 hours was determined following *aminonaphthol sulfonic acid method*[25)], normal level of which being 246 to 500 mg/sq m, 360 mg/sq.m on an average[31)].

e) Calcium Clearance and Phosphorus Clearance

Calcium and phosphorus clearances were calculated from the following formula using the data obtained in the above.

$$\text{Clearance} = \frac{UV}{P} \times \frac{1.48}{A}$$

Normal $Cca = 1.7 \pm 0.19$ cc/min[31)].

Normal $Cp = 10.8 \pm 2.7$ cc/min[46)].

V = volume of urine per minute P = calcium or phosphorus content in blood

U = calcium or phosphorus content in urine, mg/dl

A = superficial width of body, m^2

f) Tubular Reabsorption of Phosphate (abbreviated to T. R. P., hereafter)

Following the method of CHAMBERS[11)], after micturition in the early morning 500 cc of water was orally administered at 6.00 a. m. and urine was collected until 10.00 a. m. On the other hand, blood was taken at 8.00 a. m. in which phosphorus and creatitine contents were determined, and T. R. P. was calculated form the following formula.

$$\% \text{ T. R. P.} = 100 \times \left(1 \times \frac{Up \times Sc}{Uc \times Sp}\right)$$

Up = urinary phosphorus content, mg/dl

Uc = urinary creatinine content, mg/dl

Sp = serum phosphorus content, mg/dl

Sc = serum creatinine content, mg/dl

Normal T. R. P. is 85 ± 5 per cent according to Chambers[12)], 83.3 ± 5.14 per cent according to SONODA[67)], and 95 ± 5 per cent according to FUJITA[40)]. In the present experiment, T. R. P. value lower than 80 per cent was considered to be pathological.

g) Theoretical Renal Phosphorus Threshold (abbreviated to T. R. P. T., hereafter)

Following the method of HYDE et al[41)]., 150 cc of phosphate buffer solution of pH 7.4 was infused in drip spending 90 minutes. Urinary and serum phosphorus during 30 to 60 minutes after the commencement of the infusion and 60 to 90 minutes after the commencement of the infusion were determined and intermediate reabsorption phosphorus threshold was obtained from the following formula. T. R. P. T. was ultimately obtained as an average value of the intermediate threshold of 30 to 60 minutes and 60 to 90 minutes.

$$T = S - \frac{U}{0.26}$$

S = serum phosphorus content, mg/dl

U = urinary phosphorus content per minute, mg/min.

Phosphate buffer solution for drip infusion was consisted of 1,000 cc of distilled water, 11.49 g of NaH_2PO_4-$2H_2O$ and 44.31 g of $NaHPO_4$ $2H_2O$, and the solution was desinfected for 30 minutes at 100 °C before use.

This buffer solution contained 1 per cent of non-organic phosphorus with pH 7.4, 100 cc of which was mixed with 400 cc of saline solution and infused in drip. Its normal value was 2.6 to 4.2 mg/dl (3.5 ± 0.47 mg/dl)[67].

iv. Histological Studies

Fixation and staining of sections: Besides the part of ulceration, the duodenum, the pyloric portion and the corpus of the stomach of the operatively extirpated specimens were fixed in 10 per cent formalin solution and stained doubly with hematoxylin and eosin, the sections further being stained with periodic acid and P. A. S. reaction was carried out following SCHIFF[37)51)].

2. Results

A. Peptic Ulcer and Acidity of Gastric Juice

i. Acidity of Gastric Juice and Length of Disease Period in Cases of Peptic Ulcer

During 5 years since 1959, there were 137 cases of gastric ulcer and 54 cases of duodenal ulcer, both of these ascertained operatively (Tab. 1). Among these, 65 cases, 47 per cent of gastric ulcer and 11 cases, 20 per cent of duodenal ulcer revealed low value of acidity of gastric juice. Concerning the correlation between the length of disease period and the acidity, it cannot be said that the longer the disease period, the lower the acidity was.

ii. Acidity of Gastric Juice and Concomitant Gastritis

Among 52 cases of gastric ulcer, intense concomitant gastritis was observed in 37 cases, 71 per cent (excluding superficial gastritis). Out of these 37 cases, there were as many cases as 14, in 38 per cent, which showed normo- or hyperacidity of gastric juice. Out of 14 cases in which concomitant gastritis was hardly observed, gastric juice revealed hypo- or anacidity in 5 cases, in 35 per cent. Concerning the relationship between the

Tab. 1 Acidity of Gastric Juice and Interval between Onset of the Disease and Operation

Gastric Ulcer (137 Cases)

Acidity	%	Interval between Onset of the Disease and Operation %			
		1–6 months	7–12 months	1–5 years	over 6 years
Hyperacidity	21.2	27.7	27.7	27.7	16.9
Normoacidity	31.6	15.6	21.9	43.7	18.8
Hypoacidity	47.2	32.6	20.4	34.7	12.3

Duodenal Ulcer (54 Cases)

Acidity	%	Interval between Onset of the Disease and Operation %			
		1–6 months	7–12 months	1–5 years	over 6 years
Hyperacidity	44.4	41.0	6.5	46.0	6.5
Normoacidity	35.5	41.6	33.3	25.1	0
Hypoacidity	20.0	22.2	22.2	22.2	33.4

acidity in duodenal ulcer and concomitant gastritis, gastric juice revealed normo or hyperacidity in 8 cases out of 9, in 88 per cent, in which the degree of concomitant gastritis was considered to be intense, hyperacidity being observed only in remaining 1 case (Tab. 2). Hypoacidity of gastric juice was observed in 2 cases out of 12, in 16 per cent, in which histological finding of the stomach was almost normal excpt the ulceration.

iii. Alkaline Secretion of the Stomach in Cases of Peptic Ulcer

As shown in Tab. 3, alkaline secretion of the stomach was constant regardless of the acidity, approximately being from 10 to 17, and there was no recognizable correlation between alkaline secretion and acidity of gastric juice, making it difficult to say that alka-

Tab. 2 Acidity of Gastric Juice and Concomitant Gastritis

Gastric Ulcer (52 Cases)

Degree of Gastritis	No. of Cases	Hyperacid.	Normoacid.	Hypoacid.	Anacid.
Normal	14	4	5	4	1
Superficial Gastritis	1	0	1	0	0
Chronic Interstitial Gastritis	9	4	2	1	2
Chronic Metaplastic Gastritis	21	0	6	9	6
Chronic Atrophic Gastritis	7	0	2	5	0

Duodenal Ulcer (21 Cases)

Degree of Gastritis	No. of Cases	Hyperacid.	Normoacid.	Hypoacid.	Anacid.
Normal	12	9	1	2	0
Superficial Gastritis	0	0	0	0	0
Chronic Interstitial Gastritis	5	3	2	0	0
Chronic Metaplastic Gastritis	3	1	1	0	1
Chronic Atrophic Gastritis	1	1	0	0	0

Tab. 3 Alkaline Secretion in the Stomach

Gastric Ulcer (10 Cases)		Duodenal Ulcer (11 Cases)		Gastritis (8 Cases)	
Acidity	Alkaline Secretion	Acidity	Alkaline Secretion	Acidity	Alkaline Secretion
Hyper.	7.8	Hyper.	9.1	Hyper.	14.7
Hyper.	17.5	Hyper.	10.3	Hyper.	16.2
Hyper.	12.3	Hyper.	12.2	Hyper.	14.5
Normo.	9.2	Hyper.	29.6	Hypo.	13.7
		Hyper.	15.0	Hypo.	5.7
Hypo.	36.8	Hyper.	31.0	Hypo.	7.7
Hypo.	13.0	Hyper.	17.8	Hypo.	15.0
Hypo.	14.1	Normo.	16.3		
Hypo.	18.1	Normo.	12.3		
Hypo.	18.6	Hypo.	17.5		
Hypo.	10.8	Hypo.	17.8		
Mean	15.8	Mean	17.1	Mean	10.9

line secretion was particularly intense in cases of hypoacidity. There was a tendency of increase in alkaline secretion rather in cases of peptic ulcer, when compared with the control.

B. Parathyroid Function in Cases of Peptic Ulcer

i. Serum and Urinary Calcium Levels

Both serum and urinary calcium showed only a fluctuation within the physiological range, revealing no significant difference compared with control cases (Tab. 4, Fig. 1 and 2).

ii. Serum and Urinary Phosphorus Levels

In some cases of peptic ulcer, serum phosphorus was slightly lower, revealing, however, no significant difference compared with the control (Tab. 4, Fig. 3). Urinary phosphorus level was within normal range (Tab. 4, Fig. 4).

iii. Calcium Clearance and Phosphorus Clearance

Both clearances were within normal range, revealing no significant difference compared with the control (Tab. 4, Fig. 5 and 6).

iv. % T. R. P.

There were some cases showing considerably low value of % T. R. P. in the group of peptic ulcer, i. e. 7 cases out of 38, in 18.4 per cent, % T. R. P. was less than 80 per cent and in 1 case out of 12 of gastritis, % T. R. P was 8 per cent. There were many cases showing obviously low value of % T. R. P. in group of peptic ulcer whereas such low value could not be observed in any case of the group of other miscellaneous

Tab. 4 Parathyroid Function I. Gastritis

Cases	Acidity	Phosphorus		Calcium		Phosphorus Clearance	Calcium Clearance	% TRP
		Serum	Urine	Serum	Unine			
No. 1	Hyper.	3.37	301.0	4.4	31.5	5.15	11.14	
2		3.95						96.5
	Mean	3.82	301.0	4.4	31.5	5.15	11.1	96.5
3	Normo.	2.7	344.0	4.7	128	7.12	12.36	74.75
4		3.0	392.7	4.6	64.3	7.80	7.13	93.79
5		2.9	289.8	4.4	899	6.68	11.53	90.76
	Mean	2.86	342.1	4.5	363.7	7.20	10.34	86.43
6	Hypo.	2.3	28.8	4.6	1.2	6.11	4.43	90.3
7		3.12						95.25
8		2.8	40.0	4.5	96.8	2.62	10.07	86.31
9		1.1						94.5
10		2.2	350	4.9	276.1	9.87	28.75	82.72
11		3.2	143.3	5.2	80.8	7.62	8.64	95.87
12		3.7	410	4.3	110.2	9.78	15.02	85.25
13		4.6						96.9
	Mean	3.25	254.4	4.7	121.1	7.2	13.38	90.88
Mean		3.25	288.8	4.6	223.7	6.97	12.12	90.24

Tab. 4 Parathyroid Function II Gastric Ulcer

Cases	Acidity	Phosphorus		Calcium		Phosphorus Clearance	Calcium Clearance	% TRP
		Serum	Unine	Serum	Urine			
No. 14	Hyper.	2.4	760	4.6	33.6	8.72	3.95	96.41
15		2.8	184.6	4.6	102.2	4.55	10.00	97.19
16		2.8	133.0	5.0	34.2	3.89	2.93	94.34
17		3.1	45.0	4.7	43.0	10.56	1.84	97.29
18		2.7	475.8	4.7	190.3	7.69	17.21	93.05
19		3.95						86.1
20		3.6						89.3
	Mean	3.05	319.6	4.7	80.66	7.08	7.88	93.38
21	Normo.	2.8	323.0	5.0	110.2	6.04	12.36	97.1
22		2.4	489.0	4.6	96.4	10.21	11.59	76.84
23		3.45						81.1
24		3.15						92.07
25		3.6						86
	Mean	3.08	406.4	4.8	103.3	8.12	11.97	86.62
26	Hypo.	3.0	273.6	4.4	51.7	6.65	5.65	69.86
27		3.0	100	4.7	73.6	2.14	8.58	85.89
28		3.3	680	4.6	122.4	13.58	13.48	53.85
29		2.21	295.8	4.4	106.1	8.90	4.48	69.01
30		3.60						91.0
31		3.75						90.8
32		3.5						87.37
33		3.75						78.0
34		2.1						96.86
	Mean	3.17	367.32	4.46	88.66	7.81	8.04	80.29
35	Unknown	3.1	270	4.4	219.0			90.7
36		3.951						91.8
Mean		3.29	347.5	4.6	99.4	7.53	8.64	86.37

Tab. 4 Parathyroid Function. III Duodenal Ulcer

Cases	Adidity	Phosphorus		Calcium		Phosphorus Clearance	Calcium Clearance	% TRP
		Serum	Unine	Serum	Urine			
No. 37	Hyper.	2.3	40.8	4.5	78.4	12.15	8.07	84.74
38		3.0	150	4.3	110	3.67	13.3	91.12
39		5.25						88.94
40		3.3						90.75
41		3.37						84.20
42		3.52						92.4
43		6.0						93
44		3.45						90.5
	Mean	3.77	27.9	4.4	91.2	7.91	10.68	88.21

45	Normo.	3.5	190	4.3	70.3	1.33	9.16	91.11
46		3.9	469.7	5.0	76.9	9.56	8.52	98.69
47		3.0						90.59
	Mean	3.46	329.9	4.6	73.6	6.94	8.84	93.46
48	Hypo.	2.5	448.2	1.5	59.4			95.13
49		3.1	490	4.3	80.5	9.91	9.25	74.15
50		3.0						92.04
51		3.0						74.1
	Mean	2.9	469.1	4.4	69.9	9.91	9.23	83.83
Mean		3.47	298.1	1.48	79.2	7.92	9.66	88.76
				Peptic Ulcer (38 Cases)				
Mean		3.2	323.8	4.6	86.73	7.65	8.9	87.4

Tab. 4 Parathyroid Function. IV Other Miscellaneous Diseases

Cases	Diseases	Phosphorus		Calcium		Phosphorus Clearance	Calcium Clearance	% TRP
		Serum	Urine	Serum	Urine			
No. 52	Stomach	2.8	427.2	4.3	38.3	5.18	4.25	95.44
53	Cancer	3.33	232.	4.2	124.8	6.18	18.01	87.53
54		2.7	297.0	4.5	89.10	7.26	8.74	94.4
55		3.1	243.6	4.2	50.40	5.78	5.78	
56		3.45						85.3
57		3.95						80.1
58		4.1						91.0
59		3.30						90.1
60		4.10						85.2
61		3.45						88.8
62	Normal	2.8	562.8	4.8	134	8.10	1.25	94.33
63		2.7	440	4.5	168.5	11.31	15.92	90.90
64		2.7	52.8	5.0	140.8	10.13	14.66	91.07
65		2.9	390	5.0	97.2			84.57
66		3.45						98.4
67		4.75						94.6
68		4.10						96.2
69	Banti's	2.5	211.8	4.3	93	7.8	9.94	87.54
70	Disease	3.9						89.8
71	Appendicitis	2.9	470	4.7	71.4	8.88	7.49	95.01
72	Cholecystis	2.6	532	4.5	133.0	13.02	11.72	90.28
73	Pancreatitis	3.07						86.51
Mean		3.30	396.7	4.51	103.68	8.34	9.77	90.32

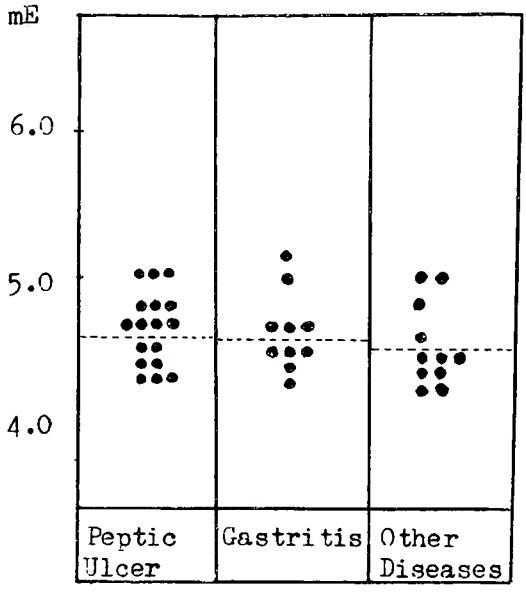

Fig. 1 Serum Celcium

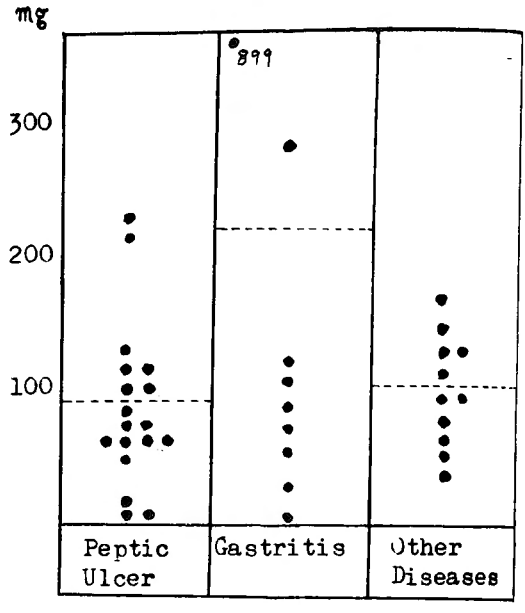

Fig. 2 Urinary Calcium

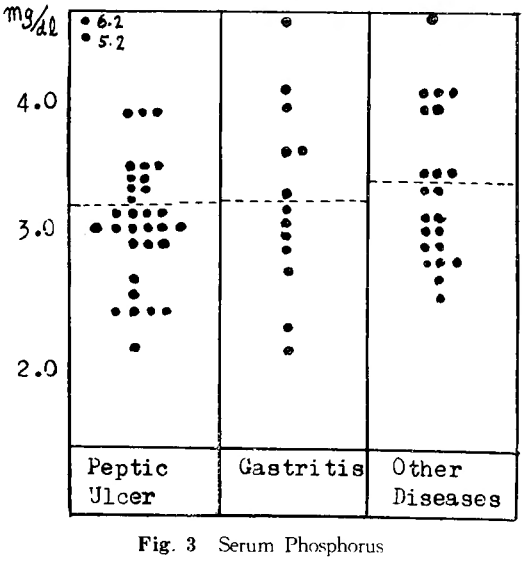

Fig. 3 Serum Phosphorus

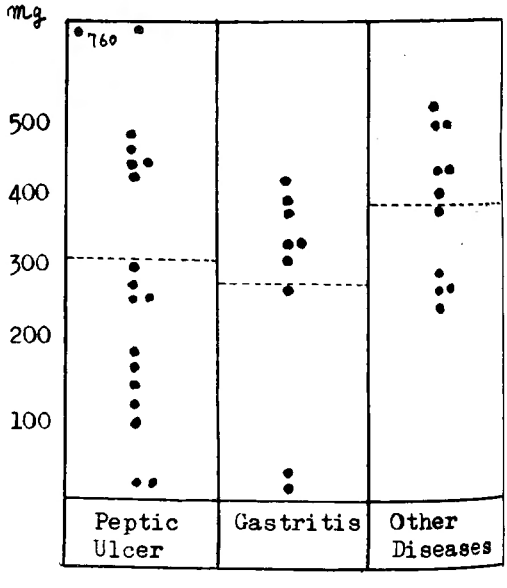

Fig. 4 Urinary Phosphorus

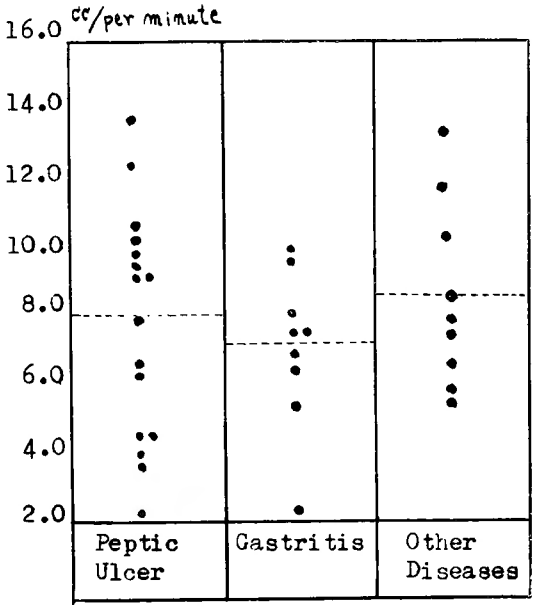

Fig. 5 Phosphorus Clearance

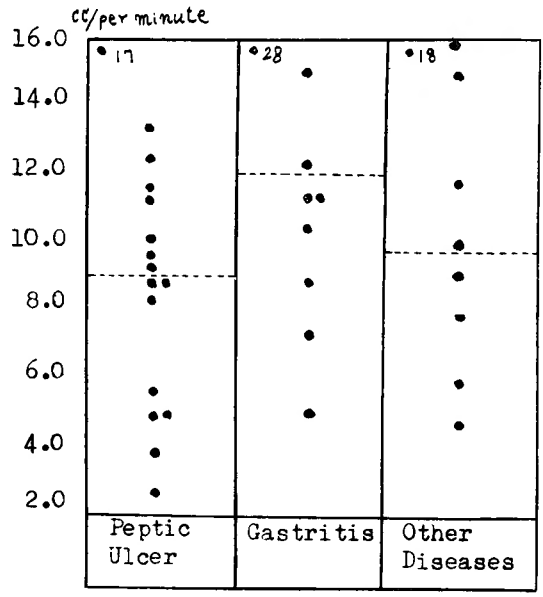

Fig. 6 Calcium Clearance

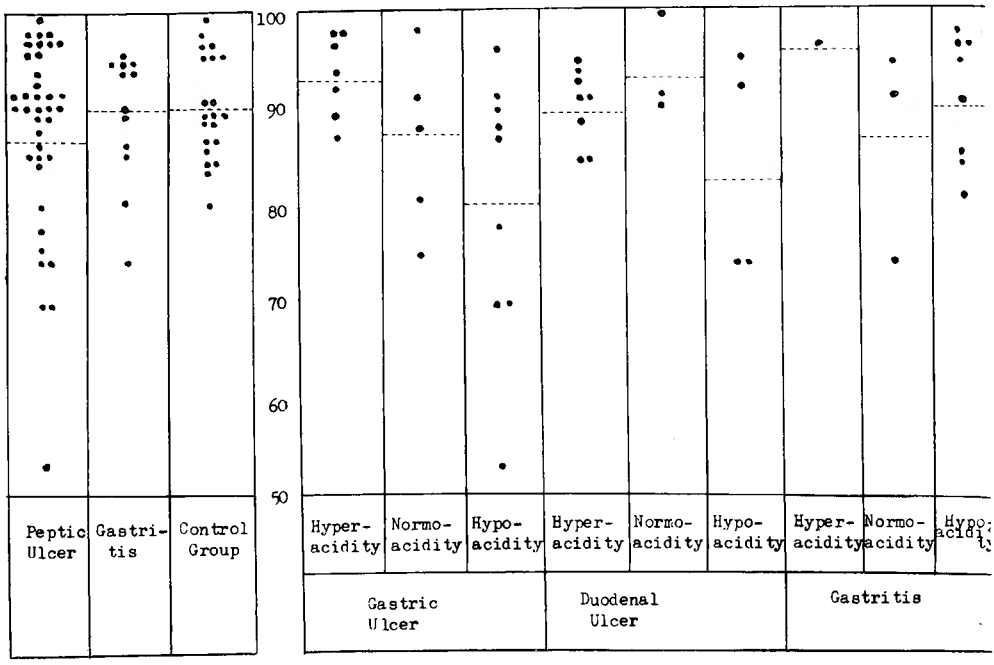

Fig. 7 Relationship between % T. R. P. and Acidity of Gastric Juice in 38 Cases of Peptic Ulcer, 12 Cases of Gastritis and 21 Cases of Other Diseases.

diseases (Tab. 4, Fig. 7). In Fig. 7, % T. R. P. value of the group of peptic ulcer is classified in relation to acidity of gastric juice. As obviously understood from the Fig. 7, % T. R. P. was almost normal in cases with hyperacidity. On the contrary, most of cases revealing lower % T. R. P. were included in those with hypoacidity. From the aspect of average value also, it was as low as 87.4 per cent in group of peptic ulcer, when compared with the values of 90.2 per cent in group of gastritis and 90.3 per cent in group of other miscellaneous diseases. Although it is generally said that peptic ulcer associated with the parathyroid hyperfunction frequently occurs in the duodenum, there could not be found any difference in the incidence of ulceration between the stomach and duodenum in clinical observation in the present study.

v. % T. R. P. and T. R. P. T.

As shown in Tab. 5 and Fig. 8, there was a tendency that % T. R. P. was low in cases with low T. R. P. T. and % T. R. P. was high in those with high T. R. P. T., although outstanding correlation could not be observed between these two.

C. Histological Findings

i. Hematoxylin and Eosin Staining

In the area of ulceration, a layer of granulation and scarring at the bottom were observed. Although in some part of gastric mucous membrane in the area other than ulceration, metaplasia of gastric gland into epithelium of intestinal gland was recognized, there was not any marked difference between those cases with hyperfunction and hypofunction of the parathyroid, particularly between those with low % T. R. P. and with high % T. R. P.

Tab. 5 Relationship between TRPT and % TRP

Cases	Diseases	TRPT	30–60			60–90			Urinary Phosphorus per Minute		% TRP
			Volume of Urine	Phosphorus		Volume of Urine	Phosphorus				
				Serum	Urine		Serm	Urine	30–60	60–70	
No. 32	Gastric Ulcer	2.45	300	9.4	66.7	290	9.52	65.3	6.67	6.54	87.37
25	Gastric Ulcer	4.83	95	10.63	176.25	102	13.2	235	5.80	8.23	86.0
40	Duodenal Ulcer	3.23	155.6	8.65	58.4	170	9.9	113	3.03	6.40	90.75
47	Duodenal Ulcer	3.08 2.90	120	10.5	178	130	9.4	145	7.12	6.24	90.59
50	Duodenal Ulcer	3.64 2.16	20	7.7	580	33	9.1	632	3.87	6.95	92.04
51	Duodenal Ulcer	2.61	170	7.7	57	165	7.65	88	3.25	4.84	74.0
42	Duodenal Ulcer	2.99 2.37	30	8.15	497	39	10.5	600	5.16	8.13	92.4
7	Gastritis	5.15	50	9.15	226	125	9.9	154	3.84	6.42	95.25
41	Duodenal Ulcer	2.54 1.89	110	8.9	166.5	100	7.78	227.1	6.105	7.58	84.20

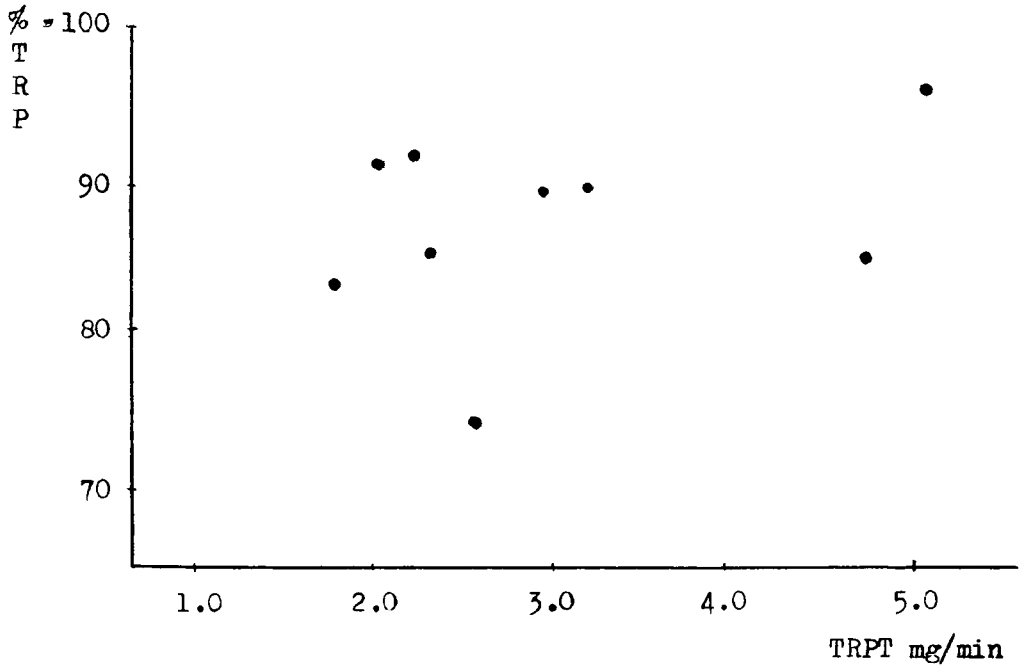

Fig. 8 Relationship between % TRP and TRPT

ii. P. A. S. Staining

Histological findings of P. A. S. staining in cases with low value of % T. R. P. showed complete disappearance of P. A. S. positive substance in the bottom of the ulceration and decrease in P. A. S. positive granules both in covering epithelium and gastric gland in the marginal area of the ulceration with marked atrophic change. However, in these findings significant difference could not be observed when compared with those in cases with presumably normal function of the parathyroid (Photo 1).

D. Summary

Gastric juice in cases of peptic ulcer was hypoacidity in 47 per cent of gastric ulcer and 20 per cent of those of duodenal ulcer. Concerning the length of disease period and the acidity, it was not recognizable that the longer the disease period, the lower the acidity was. It was also difficult to conclude that all cases with the lower acidity of gastric juice had concomitant gastritis of an intense degree. The result of determination of alkaline secretion was hardly prominent in cases with hypoacidity. Examinations on parathyroid function in these cases of peptic ulcer revealed no abnormality in serum phosphorus and calcium, urinary phosphorus and calcium and phosphorus clearance and calcium clearance. However, in % T. R. P., there were many cases which showed obviously lower value in group of peptic ulcer when compared with that in the control study, and in addition, most of those cases with low % T. R. P. were included in cases with hypoacidity. Accordingly, it is presumed that there exist some cases of hyperparathyroidism among those with hypoacidity. Moreover, histological studies with hematoxylin and eosin staining and histochemical studies with P. A. S. staining were carried out in the area of ulceration and

its margianl part of the stomach specimens extirpated from the patients presumed to have hyperfunction of the parathyroid. However, there was no significant difference in these findings between these cases and those[53] of peptic ulcer with normal parathyroid function.

III. EXPERIMENTAL STUDIES

From the above described results of clinical observations, it was presumed that there exist some cases of hyperparathyroidism closely relating to the ulceration among those of peptic ulcer, particularly those with hypoacidity of gastric juice. Here, the study was carried out to investigate the influence of experimental administration of parathyroid hormone on the occurrence of gastroduodenal ulcer. COLLIP[15], HAUPER[35], CANTAROW[10] and others[50] observed hemorrhage and erosion in the stomach and other organs of animals died from excessive administration of parathyroid hormone. In the present experiment, parathyroid hormone of certain dosis, which does not cause marked general disorders such as lethal intoxication, was administered in rats and rabbits, and the changes in the stomach and duodenum caused by this hormone were pursued.

1. Materials and Methods

i. Experimental Animals

One hundred and twenty-one male rats of Whister strain of 80 postnatal days weighing about 90 to 110 g and 2 months aged 16 rabbits weighing about 2.0 to 2.5 kg were used, rats being fed by Oriental Solid Diet and plentiful water and rabbits being fed by bean-curd leavings and vegetables arbitrarily.

ii. Parathyroid Hormone

Parathyroid Hormone of Wilson Co. 50 U. S. P. units/cc was used.

iii. Administration of Parathyroid Hormone

a) Rat

In rats, parathyroid hormone was administered subcutaneously or intravenously. Animals for subcutaneous administration were divided into 8 groups of 10 rats in each, receiving 40 units of the hormone everyday for 7 days, 280 units in total, 5 rats receiving 50 units everyday for 10 days, 500 units in total, 5 rats receiving 50 units everyday for 14 days, 700 units in total, 23 rats receiving 100 units everyday for 7 days, 700 units in total, 15 rats receiving 100 units everyday for 10 days, 1,000 units in total, 10 rats receiving 150 units everyday for 7 days, 1,050 units in total, 5 rats receiving 200 units everyday for 10 days, 2,000 units in total and 38 rats for the control study, 28 of which receiving subcutaneous injection of saline in the back and the remaining 10 rats receiving subcutaneous injection of 1 per cent $CaCl_2$ solution, being prepared by diluting 2 per cent solution with saline of one part, everyday for 7 days in the back for the control of calcium fluctuation after the administration of parathyroid hormone. Intravenous administration was carried out into the tail vein everyday for 7 days in 5 animals with a dosis of 50 units per day, 350 units in total. For the control study, saline of 1 cc was injected into the tail vein everyday for 7 days in 5 rats.

b) Rabbit

In rabbits, parathyroid hormone was administered for longer period. Namely, subcutaneous injection of the hormone was continued for 55 days everyday with a dosis of

100 units per day, total amount reaching as much as 5,500 units. For the control study, subcutaneous injection of 2 cc of saline per day was carried out for 55 days everyday in 7 rabbits.

iv. Examination of Gastric Juice

Examination of gastric juice was invariably carried out on the gastric content in the state of animals' fill. For determination of pH of gastric juice, Toyo Test Paper (Thymol Blue pH 1.2 to 2.8, Brom-Phenol Blue pH 2.8 to 4.4) was used.

v. Histological Studies

Similarly to the above described clinical studies, hematoxylin and eosin double staining and P. A. S. staining were performed.

2. Results

i. Acidity of Gastric Juice in the State of Experimental Hyperparathyroidism in Rats

As shown in Tab. 6, gastric content after adequate feeding showed approximately constant pH of 1.8 to 2.4 both in experimental and control group, disclosing no difference between these two. It could not be concluded at least that acidity of gastric juice increases by the administration of parathyroid hormone.

ii. Fluctuation of Body Weight in Rats under Administration of Parathyroid Hormone

As shown in Tab. 7, body weight at slaughter in animals of successive 7 days' injection, 100 units per day, 700 units in total, in those of successive 10 days' injection, 100 units per day, 1,000 units in total and in those of successive 7 days' injection, 150 units per day, 1,050 units in total showed slight tendency of decrease due to administration of parathyroid hormone. However, the decrease was as slight as 7 per cent on the average of all cases at slaughter, and it is difficult to assume that the administration of parathyroid hormone seriously affected the nutritional condition when considered from the aspect of body weight.

Tab. 6 Relationship between Acidity of Gastric Juice and Doses of Parathyroid Hormone in Rats

Parathyroid Hormone of 700 μ		Parathyroid Hormone of 1050 μ	
Experimental Group	Control Group	Experimental Group	Control Group
3.2	2.0	1.8	2.2
2.2	3.0	1.8	1.8
2.4	1.6	2.0	2.2
2.2	2.4	2.4	
3.0	3.2	2.0	
2.0	1.8	2.0	
1.8	2.4	2.2	
3.4	3.0		
2.2			
3.0			
2.4			
3.0			
Mean 2.6	2.42	Mean 2.03	2.06

Tab. 7 Fluctuation in Body Weight of Rats Receiving Subcutaneous Administration of Parathyroid Hormone (Body Weight at Autopsy Slaughter)

	100 μ × 7	100 μ × 10	150 μ × 7
Experimental Group	109.5	120	85
	89.5	116	83
	79.4	105	94
	91.7	122	101
	79.5	136	94
		97	96
			98
Mean	89.9	116	93.3
Control Group	98.2	100	112
	95.5	139	89
	91.0	125	98
		134	
Mean	94.9	121.5	99.6

Prior to experiment, bodyweight ranged from 85 to 115 g, 95.0 g on the average, which became, at the end of experiment, 99.7 g on the average in experimental group and 106.3 g on the average in control group.

iii. Occurrence and Incidence of Pathologic Changes in the Gastro-Duodenal Mucous Membrane in the State of Experimental Hyperparathyroidism in Rats

There was little change macroscopically in the group of successive 7 days' injection of 40 units per day as well as in control, while dotted petechia could be observed in the glandular stomach of 3 animals out of 5 in successive 10 days' injection of 50 units per day. In the group of successive injection for 14 days, 50 units per day and 700 units in total, particular change could not be observed as in control animals. However, even if the total amount was similarly 700 units, among 23 animals with successive 7 days' injection of 100 units per day, petechia were observed in 3 animals, hemorrhagic erosion in 1 case and material loss of the mucous membrane in the entrance of the duodenum in 3 cases. In all these cases, the stomach was generally edematous and hyperemic with dilatation of the vessels. Among 15 animals of successive 10 days' injection of 100 units per day with total amount of 1,000 units, petechia were observed in 1 case, hemorrhagic erosion with coffee residuum-like blood filling the stomach in 2 cases and material loss of the mucous membrane on the border of the stomach and duodenum. In this group, the incidence of erosion was the highest to be 20 per cent. Among 10 animals of successive 10 days' injection of 150 units per day with total amount of 1,500 units, petechia were observed in 2 cases and any changes could not be observed in animals of successive 10 days' injection of 200 units per day with total amount of 2,000 units. In animals with intravenous administration of parathyroid hormone, petechia were observed in 1 case, gastric bleeding in 1 case and changes could not be observed in control animals. Among 10 animals with the administration of 1 percent $CaCl_2$, dotted petechia were at most observed revealing no other abnormality (Tab. 8).

iv. Histological Findings of the Stomach and Duodenum of Rats under Administration of Parathyroid Hormone

Tab. 8 Changes in the Stomach and Duodenum in Rats of Experimental Hyperparathyroidism

		Total Dosis (Units)	Administration u × days	No. of Animals	Petechien	Erosion		
						Hemorrhagic Erosion	Acute Ulcer	Total %
Group of Subcutaneous Administration	Experimental Group	280	40×7	10	0	0	0	0
		500	50×10	5	3	0	0	0
		700	50×14	5	0	0	0	0
		700	100×7	23	3	1	3	4 (17%)
		1000	100×10	15	1	2	1	3 (20%)
		1050	150×7	10	2	0	0	0
		2000	200×10	5	0	0	0	0
				73	9	3	4	7
	Control Group	7-28cc	0.9% NaCl 1-4cc×7	28	2	0	0	0
		14cc	1%CaCl 2cc×7	10	3	0	0	0
Group of Intravenous Administration	Experimental Group	350	50×7	5	1	1	0	1 (20%)
	Control Group	7cc	0.9% NaCl 1cc×7	5	0	0	0	0

a) Cases of Acute Ulceration

Photo 2 shows the finding of animals with total amount of the administration of 1,000 units. In this case, material loss of the mucous membrane on the border of the stomach and duodenum was observed being accompanied by an intense hyperemia at gross observation, which was histologically demonstrated also to be acute shallow ulceration. Material loss of the mucous membrane reached as far as markedly dilated vessels in submucous proper layer, revealing hemorrhage which sever lamina muscularis mucosa (Photo 3). Although necrobiosis can be observed around the site of ulceration, fibrinoid degeneration or formation of granulation cannot be observed (Photo 4). P. A. S. staining of this section shows disappearance of P. A. S. positive granules in this area and the glandular tissue around, suggesting disturbance of the function (Photo 5).

b) Cases of Erosion

Specimen in Photo 6 shows a macroscopic dent with marked hyperemia in the duodenum 3 mm distant from the pyloric ring, which was identically duodenal mucous membrane covering the Brunner's gland, revealing desquamation of the epithelium, exposure of the interstitial tissue and severance and separation of glandular epithelium. The site of material loss in the mucous membrane is filled with mucoid substance stained red with eosin showing the finding of acute erosion (Photo 7). Disappearance of P. A. S. positive substance is observed in epithelial cells of the gland, suggesting disturbance of their function (Photo 8).

Photo 9 shows macroscopic finding of linear ulcer of 2 mm in width and 4 mm in

length in the duodenum approximately 5 mm distant from the pyloric ring being accompanied by intense hyperemia. Histologically, disappearance of the duodenal villi can be seen with necrosis of the mucous membrane reaching as far as submucous proper layer and marked deformation of nuclei and cells of the remaining glandular cells. In P. A. S. staining, P. A. S. positive substance is observed in a shape of irregular granules, at the same time revealing vacuolization, suggesting decay of the function of remaining glandular cells, if any, at the bottom of the erosion (Tab. 10).

Photo 12 shows coffee residuum-like substance filling the stomach in animal with the administration of parathyroid hormone of 1,000 units in total, histological examination of the stomach revealing the picture of hemorrhagic erosion (Photo 13). In the pyloric portion of the stomach, loss of the epithelium, exposure of the interstitial tissue and increase in the secretion can be observed, red blood cells and hemosiderin-like substance being contained in its lumen.

Fresh bleeding can be seen macroscopically in the specimen of Pho o 14, histological finding of which was superficial erosion with adherent mucus.

c) Cases without Macroscopic Changes

Photo 15 shows the enlargement of lymph follicle in the duodenum of the animal with successive 7 days' injection of 150 units per day, 1,050 units in total, and reticulum cells including hemosiderin granules can be observed in the lumen, which being found in 2 cases out of 5.

In P. A. S staining of the Brunner's gland in animals with the administration of parathyroid hormone of 2,000 units in total (Photo 16), P. A. S. positive substance in the cell body of the Brunner's gland is much more slightly stained than in control animals (Photo 17), and most of which show vacuolization, suggesting decay of the function. Such change was observed in 3 cases out of 5 without macroscopic changes. In the group of the administration of 1,000 units, decrease in the degree of P. A. S. reaction could be observed in 5 cases out of 10.

v. Changes of the Stomach of Rats with Administration of Parathyroid Hormone and Seasons

Administration of parathyroid hormone above mentioned requires some amount of the hormone exceeding certain dosis. However, the larger amount of parathyroid hormone does not always result the more frequent incidence of gastroduodenal changes, but, besides the dosis itself, factors of the seasons can be considered to participate in this process (Tab. 9). Namely, changes of the stomach of the rats receiving administration of parathyroid hormone occurred more frequently in winter from December to March, and the incidence was lower in the period from September to November. During May to August, the changes hardly occurred, even if the dosis of the administration was increased.

Tab. 9 Relationship between Occurrence of Erosion and Seasons

Total Dosis	No. of Animmals	Erosion	Dec.-Mar.	May-Aug.	Sep.-Dec.
700	23	1	3/13	0/5	1/5
1000	15	3	3/10	0/5	
1050	10			0/10	

vi. Macroscopic Changes of the Stomach and Duodenum of Rabbits Induced with Administration of Parathyroid Hormone

Parathyroid hormone was subcutaneously injected everyday for 55 days, 100 units per day and 5,500 units in total in 7 rabbits (Tab. 10). In this occasion, as the hormone of large amount was adminstered for long period, 2 animals died in the course of the experiment, one dying on 36th day and another on 46th day of the administration. Material loss of mucous membrane of the duodenum could be observed in 1 case, dying on 46th day, out of 7, in 14.2 per cent.

Tab. 10 Changes in the Stomach and Duodenum in Rabbits of Experimental Hyperparathyroidism

		Total Dosis (Units)	Administration u × days	No. of Animals	Petechien	Erosion		
						Hemorrhagic Erosion	Acute Ulcer	Total %
Experimental Group	Survival Cases	5500	100 × 55	7	1	0	1	1 (11.2%)
	Lethal Cases	4600	100 × 46	1	0	0	1	1 (50%)
		3600	100 × 36	1	0	0	0	0
	Total			9	1	0	2	2 (22.2%)
Control Group		110cc	0.9% NaCl 2cc × 55	7	1	0	0	0

vii. Histological Changes of the Stomach and Duodenum of Rabbits under Administration of Parathyroid Hormone

a) Cases of Acute Ulceration

In the animal which died when the administration reached 4,600 units in total, necrosis could be observed from the bottom of mucous membrane to serosa (Photo 18), and microscopically, necrotic zone was strongly stained blue with hematoxylin with proliferation of granulation around and that of connective tissue in serosa, revealing the picture of subacute change (Photo 19 and 20).

b) Cases of Erosion

Erosion could be observed in 1 case out of 7 with successive subcutaneous injection of parathyroid hormone for 55 days, 100 units per day and 5,500 units in total. Macroscopically, material loss in the area of the pyloric ring had the size of 3 × 3 mm with hyperemia. Histologically, desquamation of the epithelium and atrophy of the mucous membrane were characteristic (Photo 21).

viii. Summary

In hyperparathyroidism in the present experiment, elevation of acidity of gastric juice could not be observed. Erosion and acute ulceration were induced experimentally in the stomach and duodenum of rats and rabbits by the administration of parathyroid hormone, incidence of which being 12 per cent in rats, and 22 per cent in rabbits. Besides those cases with macroscopic changes, atrophy of the Brunner's gland and reduction of P. A. S. reaction could be demonstrated histologically even in cases without obvious macroscopic changes. Furthermore, the favorite site of the macroscopically observed erosion and acute

ulceration was in the duodenal mucous membrane covering the Brunner's gland. These changes occurred more frequently in winter.

IV. DISCUSSION

Since GRAVEILLIER[33] first reported the observation of peptic ulcer, there have been numerous studies on the mechanism of its occurrence. Among those studies which have been emphasized, representative ones are BÜCHNER's[6] digestion theory, KONJETZNY's[44] gastritis theory, DRAGSTEDT's[20][22] vagotony theory, CUSHING's[7] interbrain theory, VIRCHOW's[70] localized infarction theory, SELYE's[63] stress theory and endocrine theory[54] postulating the participation of the pancreas, parathyroid, adrenal gland and hypophysis. Today's most prevailing interpretation is autodigestion theory which emphasizes the increase in acidity of gastric juice as the cause of gastroduodenal ulceration. Secretory mechanism of gastric juice is explained to be consisted of cephalic phase in which the secretion is exerted by vagal stimulation, gastric phase in which the secretion is humorally stimulated by gastrin secreted from the pyloric vestibulum by extension of the gastric wall due to its content and intestinal phase in which the secretion is stimulated by gastrin-like substance from the small intestine secreted by stimulation of food. In some instances the cause of gastroduodenal peptic ulcer can be considered to consist in over-stimulation or hyperfunction of this secretory mechanism of hydrochloric acid, and recent studies of CUSHING[17] on production of peptic ulcer by stimulating the central nerves are widely known. It can be presumed that the acidity of gastric juice increases relatively when physiologically existing neutralization is reduced. 1) Alkaline defence seen in the mucous membrane of the cardia and pylorus, and mucus which protects the mucous membrane mechanically and is excreted from the Brunner's gland in the duodenum and 2) chemical neutralization of gastric juice by duodenal juice, pancreatic juice and bile are all considered to be physiological neutralization of acidity of gastric juice. It is readily supposed that reduction of such a neutralization leads to gastroduodenal peptic ulcer. Ulceration observed in the experiment of MANN and WILLIAMSON[49] was nothing but the ulceration which developed due to transporting alkaline digestive juice, which has chemical neutralization effect, into the lower intestine. Moreover, ulceration following external fistula of the pancreas observed by ELMAN and HARTMAN[23], ulceration following total pancreatectomy observed by DRAGSTEDT[20] and HONJO ulcer[39] as called by OOI[54], all these are considered to be due to reduction of the neutralization. In this respect, it is assumed that disturbed equilibrium between secretion of gastric juice and the neutralization has an important significance in occurrence of peptic ulcer.

Concerning the acidity of gastric juice in peptic ulcer, assertion of OOI[54] and others has been prevailing that in most cases of peptic ulcer gastric juice reveals hyperacidity, that when hypoacidity is demonstrated in such cases, decrease of acidity is considered to be secondary decrease in gastric secretion due to atrophy of the glandular cells which is caused by intense concomitant gastritis. Examination on acidity of gastric juice in gastroduodenal peptic ulcer in our clinic revealed that there were many cases, as a matter of course, with hyperacidity, but hypoacidity was observed in considerable frequency of 47 per cent in gastric ulcer and 20 per cent in duodenal ulcer. Hereupon, it is accordingly

considered to be important to investigate the mechanism of occurrence of peptic ulcer. In the present experiment, examinations on disease period and histological findings of concomitant gastritis in the cases of peptic ulcer with hypoacidity did not render reasonable basis to ascribe the cause of hypoacidity to concomitant gastritis. On the other hand, it is accepted that secretion from nonparietal cells of the stomach, as clarified by Glass[29] and others, neutralizes gastric hydrochloric acid and protects the mucous membrane. In the present experiment, however, it was difficult to conclude that alkaline secretion was accelerated in cases with hypoacidity of gastric juice.

Participation of the endocrine organs in the coccurrence of peptic ulcer has gradually come to be discussed in recent years. Steroid ulcer induced with the participation of adrenal steroids which is widely used in large amount clinically, or stress ulcer[21)63] is attracting the interest of researchers. According to the report of ZOLLINGER[73], most cases of peptic ulcer associated with endocrine tumors are those presumably due to non-β- cell tumor of the pancreas and, although with less frequency, those closely associated with the hyperfunction of parathyroid. In cases of peptic ulcer associated with non-β-cell tumor of the pancreas, the ulceration is considered to be due to hypersecretion of gastric juice, while in those associated with the parathyroid hyperfunction the acidity is mostly normal or rather decreased. In occasion of the latter, reduction of defence in the gastric mucous membrane is rather important in occurrence of the ulceration than hypersecretion of gastric juice, showing clear contrast in the mechanism of occurrence of peptic ulcer to those associated with non-β-cell tumor of the pancreas. As has been mentioned in the above, parathyroid function was investigated in cases of peptic ulcer without hyperacidity of gastric juice, since there were some cases of peptic ulcer with hypoacidity of gastric juice, which could not be accepted to be due to intensity of concomitant gastritis. There are some publications reporting[4)8)61] hypoacidity of gastric juice in animals with administration of parathyroid hormone, and there are also some investigators[72)73] who reported that gastric juice of the patient with hyperparathyroidism revealed hypoacidity. ROGERS[58] first reported 2 cases of duodenal ulcer being accompanied by hyperparathyroidism, which was followed by many reports of the same observation of St. GOAR[68], BLACK and ZIMMER[5], HELLSTRÖM[36] COPE[13] and many others,[30)56)71], and it is said that peptic ulcer associated with parathyroid hormone occurs mostly in the duodenum[45]. On the other hand, FRAME and HANDBRICK[26] studied parathyroid function in clinical cases of peptic ulcer, and in recent years, FROMM[27] examined parathyroid function in 40 cases diagnosed by internists to have peptic ulcer and observed increase in calcium and phosphorus clearances and tendency of decrease in tubular reabsorption of phosphate, with significant difference from the control. In the aim of examining parathyroid function, it is important to determine the amount of the hormone directly[18]. However, there is no credible method for the determination established yet. To survey the literatures, among many examinations on the parathyroid function, calcium loading test of HOWARD[38], % T. R. P. of CHAMBERS[11] and T. R. P. T. of HYDE[41] are said to indicate the function best. As obviously understood from the assertion of ALBRIGHT[1] that tubular reabsorption of phosphate is depressed by parathyroid hormone and from the clinical fact of unexceptional increase in urinary excretion of phosphorus in cases of hyperparathyroidism, it is significant to examine para-

thyroid function from the aspect of increase in urinary excretion of phosphorus. In the present experiment also, parathyroid function was examined in cases of peptic ulcer following SONODA[67]. Serum calcium and calcium and phosphorus clearances showed merely fluctuation within the normal range, whereas tubular reabsorption of phosphate was lower in some cases, most of which being included in those with hypoacidity of gastric juice. Accordingly, it is assumed that among those cases of peptic ulcer with hypoacidity of gastric juice there exist some cases associated with the parathyroid hyperfunction. According to the experiment of ENGEL[24] and SELYE[64], it is clarified that parathyroid hormone has the effect of depolymerizing the ground substance of the tissues. Hence, OSTROW [55] and REIFENSTEIN[57] presumed that parathyroid hormone has proteolytic action on the gastric wall as well as on the bones. As was demonstrated in the experiment of ENGEL[24], it is considered that the degree of depolymerzation[28][37] of the ground substance can be recognized by the method of P. A. S. staining. In the present experiment, P. A. S. staining was carried out in the sections from extirpated stomach[53]. However, there was no difference in the finding of the bottom of the ulceration in cases with normal parathyroid function and those with functional disturbances, in both occasions P. A. S. positive substance completely disappearing. Here, the hyperparathyroidism was experimentally induced and its influence on the stomach and duodenum was studied. Since COLLIP[14] has succeeded in 1925 in extraction of parathyroid hormone, action of this hormone has been gradually clarified[52][69], and the studies on the relationship between parathyroid hormone and peptic ulcer have been carried out also. Concerning the effect of this hormone on the acidity of gastric juice, BABKIN[4] and SCHIFFRIN[61] observed a decrease in secretion of gastric juice and hydrochloric acid and increase in pepsin in PAVLOW dog. They further reported that hyper-secretion of gastric juice observed after experimental extirpation of the parathyroid could be reduced by the intravenous administration of calcium, and they concluded that hypercalcemia caused by parathormone administration results in reduction of gastric secretion by inactivating the vagus. BLAUSHARD[8] observed slight decrease in acidity of gastric juice in his experiment of administration of parathyroid hormone in rats with ligation of the pylorus[65]. ALLEN and ELLIOT[2] stated that gastric secretion decreased during the administration of parathyroid hormone, whereas with the cessation of the administration the secretion sometimes increased showing rebound phenomenon in the experiment on HEIDENHEIN dog. Recently, DONEGAN[19] reported, on the contrary, that there was a stadium of hypersecretion in his experiment of administration of parathyroid hormone of small dosis. However, in clinical cases of chronic hyperparathyroidism, be could not recognize significant difference in the response of gastric secretion before and after removal of the parathyroid. ZOLLINGER[73] asserted that administration of parathyroid hormone does not affect the gastric secretion, but the secretion and acidity decrease when serum calcium becomes less than 7 mg/dl owing to the shortage of parathyroid hormone. In the present experiment, from the determination of acidity of gastric juice of rats after feeding, it could not be accepted that the acidity was elevated by the administration of parathyroid hormone. Concerning the experiments on the changes in the stomach and duodenum in the state of hyperparathyroidism, there are many literatures of COLLIP[15], HAUPER[35], CANTAROW[10], LEHR-MARTIN[47][48] and others[50] reporting findings of hemor-

rhage, erosion, necrosis and infiltration of calcium, and furthermore, material loss of the mucous membrane in rats with the ligation[65] of the pylorus is reported by BLAUSHARD[8]. Most of these are not, however, so well studied histologically and animals in these experiments frequently died of intoxication of the hormone by the administration of large dose within short period, necropsy revealing hemorrhage and necrosis in the various organs as well as gastric bleeding and erosion. In the present experiment, various pictures from erosion to acute ulceration could be successfully observed following the administration of the hormone. In rats acute ulceration occurred at the gastroduodenal in junction, and in rabbits layer structure of ASKANAZY[3] could be observed in subacute ulceration occurred in the similar site. Erosion mostly appeared in the oral side of the duodenum, necrosis in some cases reaching as far as the proper muscle layer. Both ulceration and erosion had a tendency to appear more frequently in winter. Similarly to the clinical studies, P. A. S. staining was performed in order to clarify its mechanism of action on the basis of hypothesis of OSTROW[55] and REIFENSTEIN[57]. The degree of P. A. S. reaction was decreased in the site of erosion, and destruction or vacuolization could be further observed in the mucous membrane remaining in the bottom of this site, suggesting lowering of the function. Particularly, in most cases of erosion and acute ulceration, decrease in and destruction of P. A. S. positive substance in the Brunner's gland could be observed. This change was observed even in cases showing no macroscopic erosion or acute ulceration after administration of parathyroid hormone. Accordingly, besides the hypothesis of REIFENSTEIN and others that parathyroid hormone has proteolytic action on the mucous membrane and reduced the defence with resulting ulceration, it is assumed that there is a possibility of occurrence of such changes in the duodenum owing to the relative increase in acidity within the duodenum which is caused by reduction of neutrallzation of acidity of gastric juice due to decrease in alkaline secretion on the basis of above mentioned changes in the Brunner's gland brought about by the administration of parathyroid hormone.

V. SUMMARY AND CONCLUSION

1) In 191 cases of gastroduodenal peptic ulcer operatively ascertained in our clinic during the past 5 years, examinations were carried out preoperatively on gastric juice by fractional collection method. Gastric juice of 65 cases out of 137 of gastric ulcer, 47 per cent, and 11 cases out of 54 of duodenal ulcer, 20 per cent, revealed hypoacidity, which did not have any correlation to the length of disease period or intensity of concomitant gastritis.

2) Examination on parathyroid function in these clinical cases revealed that among these cases of peptic ulcer, some cases showed hyperfunction of the parathyroid, particularly the decrease in tubular reabsorption of phosphate, and these cases were included in those of normoacidity or hypoacidity.

3) Gastric juice of rats in the state of experimental hyperparathyroidism did not reveal increase in acidity of gastric juice.

4) Pictures of various degree from erosion to acute ulceration could be observed in rats and rabbits with experimental hyperparathyroidism. In the rats with the administration of parathyroid hormon of 700 units in total, these pathological changes were observed

in 4 cases out of 23, in 17 per cent, in rats with 1,000 units of this hormone in total, in 3 cases out of 15, in 20 per cent, and in rabbits with the administration of more than 3,000 units in total, in 2 cases out of 9, in 22 per cent.

5) Such changes described above most frequently occurred in the oral side of the duodenum, which coincided so well with the clinical observation that peptic ulcer associated with hyperparathyroidism is frequently found in the duodenum.

6) From the findings of P. A. S. staining, dysfunction of the Brunner's gland was peresumed, besides the reduction of the degree of P. A. S. reaction of the mucous membrane. It is presumed from there findings that there exists some correlation between the occurrence of peptic ulcer and reduction of defence of the duodenal mucous membrane against hydrochloric acid due to decrease in alkaline secretion of the Brunner's gland.

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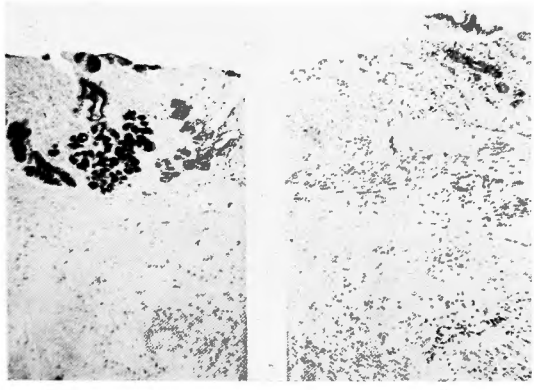

Photo 1 A Clinical Case of Gastric Ulcer Showing 74% of % TRP. Right: Disappearance of PAS Positive Granules at the Bottom of Uleration.
Left: Marked Decrease in Glandular PAS Positive Granules at the Marginal Area of Ulceration. (P.A.S. ×100)

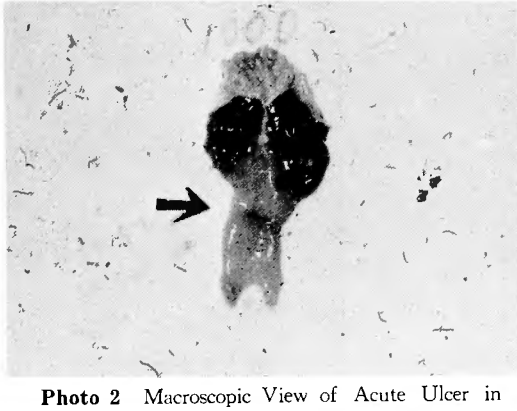

Photo 2 Macroscopic View of Acute Ulcer in Rat, Demonstrating Linear Material Lose on the Border of Pyloric Portion and Duodenum Crossing Lesser Cavarture in the Right Angle.

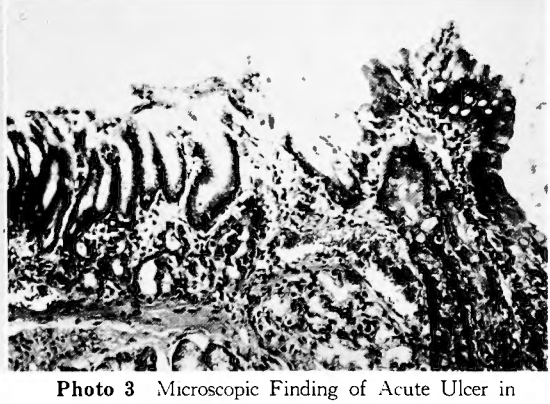

Photo 3 Microscopic Finding of Acute Ulcer in Rat, Ulceration Reaching Submucous Proper Muscle Layer. (H. E. ×150)

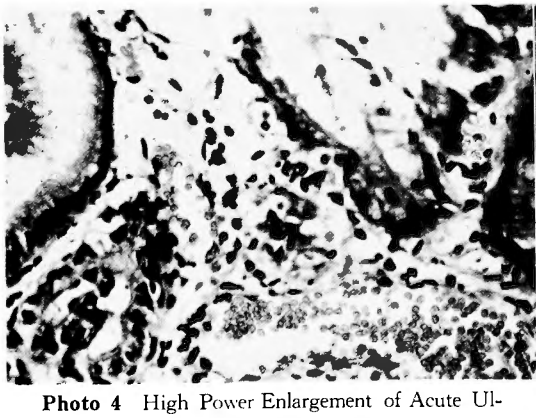

Photo 4 High Power Enlargement of Acute Ulcer in Rat, revealing Emigration of Red Blood Cells from Dilated Vessels into Gastric Lumen. (H. E. ×300)

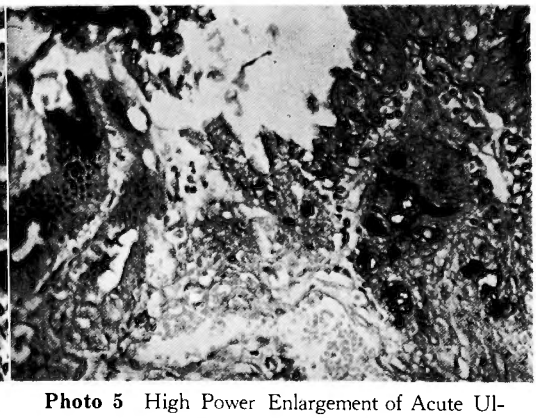

Photo 5 High Power Enlargement of Acute Ulcer in Rat, Showing Discontinuance and Irregular Shape of P.A.S. Positive Granules in Overlying and Glandular Epithelium Remaining Around Ulceration. (P. A. S. ×300)

Photo 6 Macroscopic View of Acute Ulcer in Rat.
Right: Hypermia and Material Loss in Oral End of the Duodenum.
Left: Control Animal.

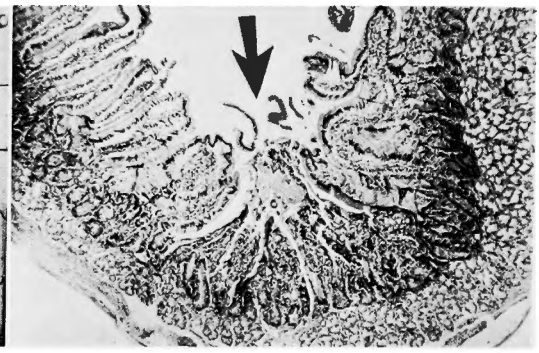

Photo 7 Microscopic Finding of Erosion in Rat Above Brunner's Gland, Containing Eosin Positive Mucous-like Substance within Interstitial Tissue. (H. E. ×50)

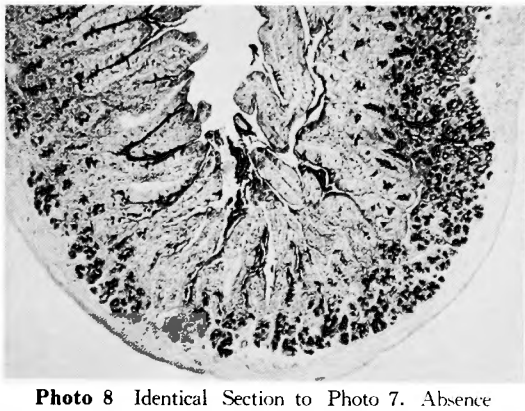

Photo 8 Identical Section to Photo 7. Absence of P. A. S. Postitive Granules in the Exposed Interstitial Tissue and Vacuolization of the Brunner's Gland. (P. A. S. ×50)

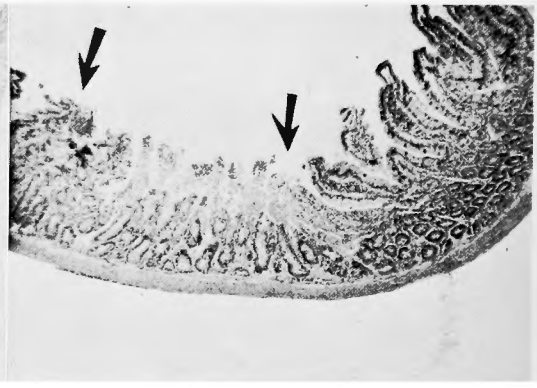

Photo 9 Microscopic Finding of Erosion in Oral End of Duodenum in Rat. (H. E. ×100)

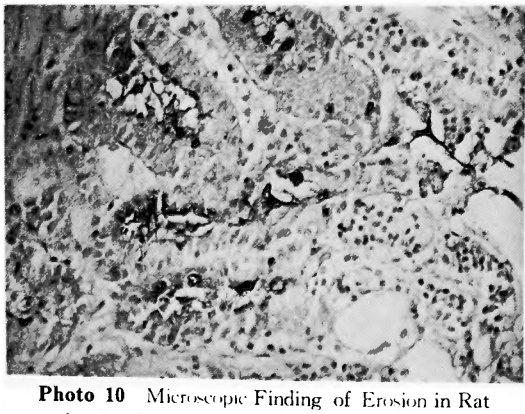

Photo 10 Microscopic Finding of Erosion in Rat showing Destruction and Discontinuance of PAS Positive Granules in Duodenal Gland Remaining at the Bottom of Erosion in the Same Section as in Photo 9. (P. A. S. ×300)

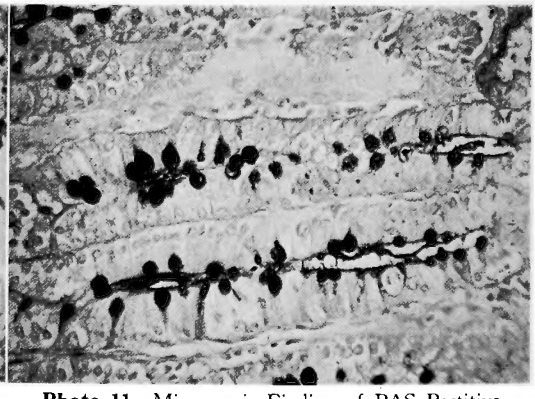

Photo 11 Microscopic Finding of PAS Postitive Granulas in Normal Duodenal Gland. (P. A. S. ×300)

Photo 12 Right : Caffee Residuum-like Substance (Aged Hemorrhage) in Gastric Lumen.
Left : Normal.

Photo 13 Microscopic Finding of Hemorrhagic Erosion in Glandular Stomach of Rat Showing Desquamation of Over-lying Epithelium, Hypersecretion Appearance of Red Blood Cells in Gastric Lumen. (H. E. ×300)

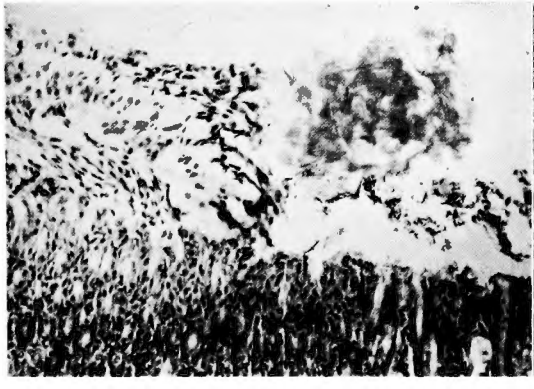

Photo 14 Microscopic Finding of Superficial Erosion in Rat, showing Adherent Mucous Consisted of Eosin Positive Mucous-like Substance. (H. E. ×150)

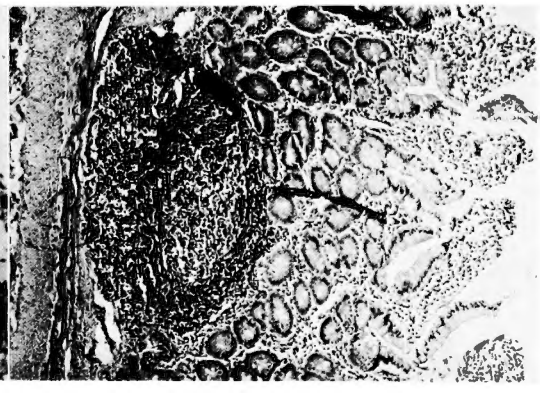

Photo 15 Enlarged Lymph Follicle in the Duodenum of Rat, Containing Reticulum Cells with Hemosiderin Particles. (H. E. ×100)

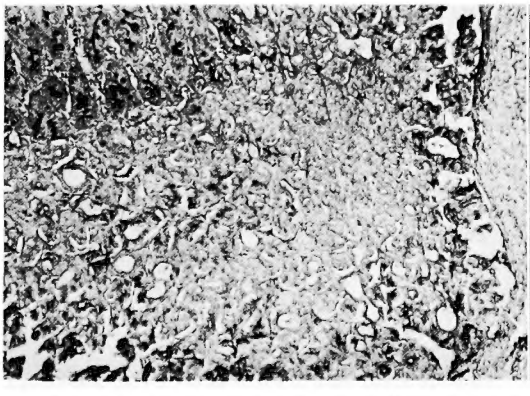

Photo 16 Brunner's Gland Vacuolization and Decrease in PAS Positive Substance in the Cells of Brunner's Gland. (Experimental Animal) (P. A. S. ×100)

Photo 17 Brunner's Gland (Control Animal) Cells of the Gland are Strongly Stained with P. A. S., being Filled with P. A. S. Postitive Granules.

Photo 18 Macroscopic view of Material Loss in Duodenum of Rabbit.

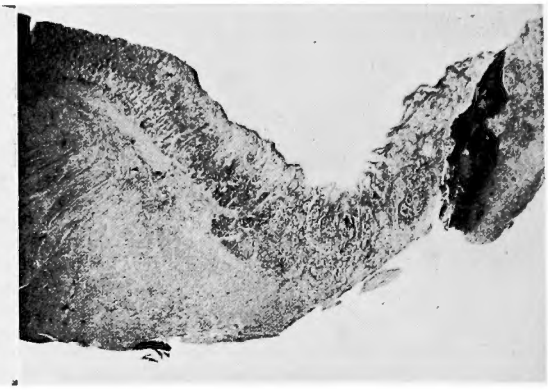

Photo 19 Microscopic Finding of Subacute Ulcer in Rabbit, Showing Necrobiosis of Mucous Membrane, Necrotic Zone strongly Stained with Hematoxylin Reaches Serosa with Proliferation of Granulation of Granulation Around.
(H. E. ×100)

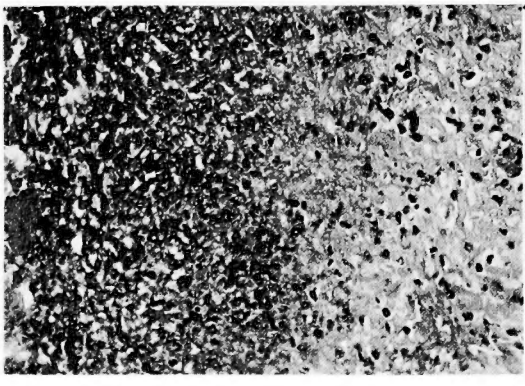

Photo 20 Transitional Part of Necrotic Zone of Photo 19, Showing Glanulation Tissue with White Blood Cells and Proliferation of Fibrocytes. (H. E. ×300)

Photo 21 Erosion in Pylonic Portion found in Slaughtered Rabbit, Showing Marked Atrophy of Mucous Membrane from the Arrow to the Arrow. (H. E. ×15)

和文抄録

消化性潰瘍と副甲状腺に関する臨床的並びに実験的研究

金沢大学医学部第2外科学教室（指導：本庄一夫教授）

渡瀬勉

消化性潰瘍の発生は胃液の酸度とこの酸に対する胃・十二指腸粘膜の抵抗機転とのアンバランスにより発生すると考えられ，特に胃液酸度の上昇を発生因子とする者が多い．一方副甲状腺機能亢進症にみられる消化性潰瘍では胃液酸度の上昇を認めないことが多く，最近注目されてきた副甲状腺機能亢進に合併する消化性潰瘍の形成機転は過酸によるというよりも，むしろ，酸に対する胃及び十二指腸粘膜の抵抗性の減弱に意義があると考えられる．私は消化性潰瘍における副甲状腺の関与につき臨床的並びに実験的に検索し，次の結果を得た．

1) 過去5年間に当科において手術的に確認された消化性潰瘍191例の手術前の胃液分割採取による検査では，胃潰瘍137例中65例47%，十二指腸潰瘍54例中11例20%に胃液酸度の低下せるものがあり，その胃液酸度の低下は病悩期間や随伴性胃炎の強弱にあまり関係がなかつた．

2) これらの症例に臨床的に副甲状腺機能検査を行なつた所，消化性潰瘍症例の中には副甲状腺の亢進，特に腎細尿管における燐再吸収率の低下を示したものが認められ，これらは胃液酸度が正常か，むしろ低下しているものに含まれていた．

3) 実験的副甲状腺減能亢進状態のラットは胃液酸度の上昇を示さなかつた．

4) 実験的副甲状腺機能亢進状態のラット及び家兎においては，糜爛から急性潰瘍に至る種々の病像を認めた．ラットでは副甲状腺ホルモン全量700単位投与した群ではその発生率23匹中4匹17%，全量1000単位投与では15匹中3匹20%で，家兎では全量300u以上で9羽中2羽22%の発生率であつた．

5) かかる変化は十二指腸始部に好発し，臨床的に副甲状腺機能亢進症における消化性潰瘍が十二指腸に好発するのとよく一致した．

6) PAS染色所見より粘膜のPAS染色態度の減退の他，Brunner氏腺の機能障害が推定されたが，この障害によつてBrunner氏腺から分泌されるといわれるアルカリ性粘液の分泌低下により十二指腸内の酸度が増加し粘膜の抵抗性の低下と共にかかる急性潰瘍を形成する一因をなしたものと思われる．

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